PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

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Date of mailing *(day/month/year)* 27 April 2006 (27.04.2006)		
Applicant's or agent's file reference ILL01-009-WO	**IMPORTANT NOTICE**	
International application No. PCT/US2004/034010	International filing date *(day/month/year)* 14 October 2004 (14.10.2004)	Priority date *(day/month/year)* 14 October 2003 (14.10.2003)
Applicant THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS et al		

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.+41 22 740 14 35	Authorized officer Athina Nickitas-Etienne Facsimile No.+41 22 338 89 95

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference ILL01-009-WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/034010	International filing date *(day/month/year)* 14 October 2004 (14.10.2004)	Priority date *(day/month/year)* 14 October 2003 (14.10.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 18 April 2006 (18.04.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/034010	International filing date *(day/month/year)* 14.10.2004
Priority date *(day/month/year)* 14.10.2003	
International Patent Classification (IPC) or both national classification and IPC C12Q1/32, C12Q1/48, G01N33/573	
Applicant THE BOARD OF TRUSTEES OF THE UNIVERSITY OF...	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/034010

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-39, 48-53
	No:	Claims	1-18, 40-47
Inventive step (IS)	Yes:	Claims	19-24, 26-32, 34-39, 48-53
	No:	Claims	1-18, 25,33,40-47
Industrial applicability (IA)	Yes:	Claims	1-53
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: CLARK B.R., HALPERN R.M. AND SMITH R.A.: "A fluorimetric method for quantitation in the picomole range of N1-Methylnicotinamide and Nicotinamide in serum" ANALYTICAL BIOCHEMISTRY, no. 68, 1975, pages 54-61,
   D2: US-A-4 166 765 (WEETALL, HOWARD H) 4 September 1979 (1979-09-04)

2. The priority documents of the present application were not available at the time that this report was written. Consequently, the document cited as PX in the I.S.R. may become relevant to the question of novelty of some or all of the claims at a later stage of the procedure.

3 The subject-matter of claim 2 is not new Art. 33(2) PCT.
Document D1 discloses a fluorimetric method for quantitation of N^1-Methylnicotinamide wherein N^1-Methylnicotinamide is converted to fluorescent derivatives by treatment with acetophenone in alcoholic KOH followed by addition of formic acid (abstract).
Document D1 further states that "the nanomolar fluorescences obtained under the same conditions for NADP+, **NAD+** and NMN+ were each approximatively 0.15" (p.57, l.6-8) and " Only N1-alkylpyridinium derivatives of nicotinamide give fluorescent products under the conditions of the assay.....NADP+, **NAD+**, and NMN+ each yield derivatives with a molar fluorescence about 1/25 that of N^1-Methylnicotinamide" (p. 61, paragraph 2).
Thus, document D1 makes it clear that the process for preparing a fluorescent derivative of N^1-Methylnicotinamide using acetophenone, KOH and formic acid has also been applied to NAD+ and the fluorescence of the compound measured.
The subject-matter of claim 2, and its dependent claims 3-5, is therefore not new (Art. 33(2) PCT).

In the view of the above, it is concluded that compound 1 as claimed in claim 1 has already been obtained in D1 which is thus prejudicial to the novelty of claim 1 (Art. 33(2)PCT).

4. For the same reasons as mentioned above under point 3, the subject-matter of claims 6 to 17 is also not new (Art. 33(2) PCT).

5. Furthermore, the subject-matter of claims 40-47 is also not new (Art. 33(2) PCT) as it is considered that D1 also implicitly discloses the kits necessary to carry out the methods disclosed therein.

6. The subject-matter of claim 18 is not new (Art. 33(2) PCT).
Document D2 discloses a method for detecting the presence of bacteria of genus Neisseria wherein the sample is tested for the presence of the enzyme 1,2-propanediol hydrogenase (an NAD+ utilizing enzyme) comprising incubating the sample with NAD+ and 1,2-propanediol (substrate) and quantifying remaining NAD+ by fluorometrically monitoring reduced NADH. Thus NAD+ has been reduced (thus converted) to a fluorescent compound (column 1, l.49-68).
Thus document D2 discloses a method of detecting an NAD+ utilizing enzyme by quantifying any remaining NAD+comprising converting the said NAD+ to a fluorescent compound (NADH).

7. Furthermore, as document D2 already discloses the concept of measuring enzyme activity by detecting and quantifying fluorescent NADH resulting from conversion of NAD+(see above), it would be obvious for the skilled man to apply this method for detecting NAD+ utilizing enzymes inhibitors or deficiencies.
The subject-matter of claims 25 and 33 does therefore not meet the requirements of Art. 33(3) PCT.

8. As the particular combination of features of claim 19 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT). Moreover, it would appear that the said claim involves an inventive step in the sense of Art. 33(3) PCT.

The closest prior art result from document D2 (see above point 6).
The subject-matter of claim 19 differs from D2 in that NAD+ is converted to the fluorescent compound 1.
The specification being silent concerning any particular effect when compared to the disclosure of D2, the technical problem can thus be formulated as the provision of an alternative non radioactive assay for detecting NAD+.

Although document D1 discloses a fluorimetric method for detecting NAD+ (see above point 3), the said document does not suggest to apply the said method to the detection of NAD+ utilizing enzymes.
Thus, all the requirements of Art. 33(3) PCT are fulfilled.

The same applies to claims 20-24, 26-32 and 34-39.

9. Similarly, as the kit of claim 48 has been specifically designed to carry out the inventive methods of claims 19-24, 26-32 and 34-39, the subject-matter of the said claim 48 and it dependent claims 49 to 53 is similarly inventive (Art. 3383) PCT).

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

2. The statement on page 1, lines 6-8 has no bearing on the invention or its background art and should thus be deleted as being irrelevant (Art.6, Rule 9.1(iv)PCT).